Biochemistry and physiology of eicosanoid precursors in cell membranes

W. E. M. Lands

National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, MD, U.S.A.

Excessive action of omega-6 eicosanoids formed from the body’s omega-6 essential fats occurs in many health disorders, and it can be diminished with dietary omega-3 fats. The current abundance of omega-6 (n-6) eicosanoid-mediated disorders (e.g. thrombotic heart attack and stroke, cardiac arrhythmia, atherogenesis, arthritis, asthma, osteoporosis, tumour metastases, etc.) accompanies n-6 acid intakes that are more than ten times than the adequate level of 0.5% of energy. The n-3 and n-6 highly unsaturated fatty acids (HUFAs) are maintained in tissue phospholipids in a competitive, hyperbolic relationship to the dietary abundance of their 18-carbon polyunsaturated fatty acid (PUFA) precursors. In contrast, 18:2n-6 and 18:3n-3 acids are maintained in tissue triacylglycerols in a linear proportion to their dietary abundance expressed as percentage of daily caloric energy. The near absence of 20:3n-9 acid in plasma phospholipids in the U.S.A. population reflects very high intakes of polyunsaturated fats that compete with oleate for conversion to tissue HUFAs. The ethnic food combinations for Greenland, Japanese, Mediterranean, and American populations give proportions of omega-6 isomers in the body long-chain acids near 30%, 50% 60% and 80%, respectively. It is of interest that these values mimic clinical outcomes associated with cardiovascular mortalities ranging from 20 to 50 to 90 to 200 per 100 000, respectively.

Therapeutic treatment to cut excessive omega-6 eicosanoid signalling has involved billions of dollars being spent to develop and market new pharmaceutical agents while a preventive nutrition approach to cut excessive omega-6 eicosanoid signalling has yet to be applied systematically in dietetics, clinical nutrition and public health. Voluntary choices of food combinations can produce proportions of omega-6 HUFAs and of omega-3 plus omega-6 HUFAs in the total body ranging from 30% to 90%, respectively. Adverse effects of excessive omega-6 eicosanoid signalling can be lowered by two interdependent dietary changes: first, reduce the daily intake of foods overly rich in the precursors of 20:4n-6 acid; and second, simultaneously increase the omega-3 PUFA's in the diet to competitively inhibit the conversion of LA into tissue omega-6 HUFAs. An interactive computer software application has been developed to combine the complex biomedical information on competitive interactions among essential fats and eicosanoids, and to interpret and display the finding in terms of multiple daily food choices understandable by the general public.

Key Words: arrhythmia, eicosanoids, food choices, thrombosis.
transitory nature fits them to an important role in modulating rapid physiological responses to stimuli. Eicosanoids (prostaglandins, thromboxanes, and leukotrienes) formed from n-6 essential fatty acids have extensively documented roles in mediating inflammatory and proliferative conditions: they enhance thrombosis, vasospasm and myocardial arrhythmia, and are potent effector molecules in asthma, transplant rejection and immune disorders. As a result, billions of dollars have been spent to develop and market new pharmaceutical agents to cut excessive n-6 eicosanoid signalling. Unfortunately, a preventive nutrition approach to cut excessive n-6 eicosanoid signalling has yet to be applied systematically in dietetics, clinical nutrition and public health.

The major dietary source of n-6 eicosanoid precursors is linoleate (18:2n-6) whereas the elongated n-6 highly unsaturated fatty acid (HUFA) arachidonate (20:4n-6), is the major immediate n-6 eicosanoid precursor maintained in tissues. Alternatively, major dietary sources for n-3 eicosanoids are linolenate (18:3n-3) and the n-3 HUFAs, eicosapentaenoate (20:5n-3) and docosahexaenoate (22:6n-3). Eicosapentaenoate is the immediate n-3 eicosanoid precursor maintained in tissues, whereas docosahexaenoate is a competitive antagonist of n-6 eicosanoid formation[3]. The impact of the different dietary essential fatty acids on eicosanoid-mediated events can be predicted from the percentage of daily caloric energy (en%) in four separate categories of essential fats: 18:2n-6, 18:3n-3, n-6 HUFAs, and n-3 HUFAs[9]. During tissue actions, the n-3 HUFAs and n-6 HUFAs maintained in cellular phospholipids are released by phospholipase action prior to forming eicosanoids[3]. Thrombotic platelet aggregation is a fatal tissue action mediated by the excessive action of the n-6 eicosanoid, thromboxane A2. Discovery of this eicosanoid was announced 25 years ago at a major international conference in Florence[6]. It was an exciting occasion for eicosanoid and medical research which led later to successful clinical trials of aspirin for reduction of heart attacks. Once the n-6 thromboxane was recognized, and its n-3 homologue was shown to be less active[7], it became important to know whether balancing the n-3 and n-6 eicosanoid precursors in tissue lipids could decrease excessive n-6 thromboxane action. We showed that supplementing diet with dietary n-3 fats decreased stroke morbidity in cats[8] and decreased myocardial infarctions in dogs[9]. We also discussed with European cardiologists[2,10,11] the possible application of this knowledge to preventive nutrition with humans. Decades later much still remains to be done to build a broader awareness of this opportunity in preventive nutrition. Ironically, the 1975 conference celebrated the success of recognizing thromboxane with its international experts gathering for a celebratory banquet at the Villa Medicea ‘La Ferdinanda’, much as the GISSI-Prevenzione Consensus Meeting 25 years later celebrated its success in reducing heart attacks with dietary n-3 fats. Many years had passed, but some progress was evident.

Eicosanoids in sudden death

The successful diminution of mortality from myocardial infarction by low-dose aspirin[12] confirmed the importance of excessive signalling by the n-6 eicosanoid, thromboxane A2, in mediating the sudden fatal event. As a result, 92% of the patients enrolled by the GISSI-Prevenzione investigators[13] had been placed on anti-platelet therapy by their physicians. Thrombosis is a platelet-mediated process in which the n-6 mediator is formed by sequential actions of phospholipase, prostaglandin synthase and thromboxane synthase. Thromboxane A2 activates thromboxane receptors, amplifying intracellular signalling that permits calcium entry associated with platelet aggregation and vascular contraction. The potent n-6 eicosanoid gives a hyperbolic response curve with maximal in vitro aggregation of platelets at about 40 ng. ml⁻¹ plasma and 50% aggregation at about 3–5 ng. ml⁻¹[14].

Possibly one-half of sudden deaths from coronary heart disease have detectable thrombi; the other half may be due to unstable electrical patterns of the heart leading to ventricular fibrillation[15]. Dietary fish oil (but not corn oil) significantly reduced myocardial ischaemic damage[16] and decreased cardiac inotropic response to alpha-adrenergic agonists[17]. Both n-3 and n-6 types of non-esterified polysaturated acids are antiarrhythmic by inhibiting channel conduction of voltage-dependent L-type Ca²⁺ currents[18,19], but the n-6 acid, arachidonic, can be arrhythmogenic by forming n-6 eicosanoids. Following inhibition of eicosanoid-forming enzymes, arachidonate was consistently antiarrhythmic like other unsaturated acids[19]. Thus, n-6 eicosanoids (but not n-3 eicosanoids) exacerbate arrhythmogenic events.

Voluntary choices of food combinations can produce proportions of n-6 HUFAs in the total body n-3 plus n-6 HUFAs ranging from 30% to 90%[4,20]. The ethnic food combinations for Greenland, Japanese, Mediterranean and American populations give proportions of n-6 in the body long-chain acids near 30%, 50% 60% and 80%, respectively. These values are surrogate clinical outcomes associated with cardiovascular mortalities ranging from 20 to 50 to 90 to 200 per 100 000, respectively[21]. This strong association combines with knowledge of the fatal mechanisms to urge more vigorous dietary efforts to decrease excessive n-6 eicosanoid action.

Maintaining n-3 and n-6 HUFAs in tissues

The n-3 and n-6 HUFAs are maintained in tissue phospholipids in a competitive, hyperbolic relationship to the dietary abundance of their C-18 PUFA precursors, as shown by Mohrhauer and Holman[22,23] and later confirmed[24-26]. The biomarkers that reflect this metabolic competition[20] also indicate nutrient status.

Eur Heart J Supplements, Vol. 3 (Suppl D) June 2001
For example, the near absence of 20:3n-9 acid in plasma phospholipids in the U.S. population reflects very high intakes of polyunsaturated fats that compete with oleate for conversion to tissue HUFA. Only after the level of 20:3n-9 acid in plasma phospholipids became greater than that of 20:4n-6 acid for several weeks were any symptoms of essential fatty acid deficiency observed[27]. In accord with these results, a dietary upper limit (UL) for 18:2n-6 acid of 3-0% of energy has been recommended[28,29]. Adverse effects of excessive n-6-eicosanoid signalling can be lowered by two interdependent dietary changes. Reduce the daily intake of foods overly rich in the precursors of 20:4n-6, and increase the n-3 fats in the diet to competitively inhibit dietary 18:2, n-6 acid from accumulating as tissue n-6 HUFA.

Making informed food choices

An interactive computer software application has been developed to combine the complex biomedical information on competitive interactions among essential fats and eicosanoids[1], and to interpret and display the funding in terms of multiple daily food choices understandable by the general public. The computerized menu planner called KIM (Keep It Managed) can be downloaded from the URL http://ods.od.nih.gov/eicosanoids. It gives information on thousands of different food servings. The interactive program calculates a surrogate clinical outcome for personal choices of daily combinations of foods by using the USDA data on C-18 n-3 and n-6 essential fats and their HUFA homologues in common foods. This software is educational for researchers, health professionals, consumers and patients by promoting ‘What if . . .’ questions and rapidly displaying the often unexpected result of a single food choice in the context of the day’s combined multiple food choices. When applied to the recommendations from a recent expert workshop[28], values of 2 en% 18:2n-6, 1 en% 18:3n-3, 0.3 en% n-3 HUFAs and 0.07 en% n-6 HUFAs produce an overall surrogate outcome of 50% of n-6 HUFA in the total tissue HUFAs (see Fig. 1 at the eicosanoids URL noted above). This value is associated with a cardiovascular mortality rate that is one-quarter of the current U.S. rate. The software allows the design of food choices for future preventive nutrition interventions that can develop sufficient long-term differences in surrogate outcomes between experimental and control groups to predict significant clinical outcomes for the overall nutrition intervention. The empirical equations and constants embedded in the software allow testing one’s expectations about how much the consistent use of a given food might influence the overall status. For example, replacing only the customary salad oil (containing over 12 000 mg of linoleate) by either canola or olive oil decreases the predicted surrogate outcome for the proportion of n-6 HUFAs from 79% to 71% or 75%, respectively. This modest decrease reflects the consequence of having started from a ‘plateaued’ value due to initial daily diets containing above 6 en% linoleate. Without competition from n-3 HUFAs, the hyperbolic pattern for the surrogate outcomes develops a half-maximal value only with linoleate intakes below 0.5 en%. However, the decreased linoleate intake with the substitute oil allows one further change of replacing a meat serving by a fish serving to produce a value near the clinical target of 50%, in a manner resembling that seen with traditional Mediterranean diets. Alternatively, using soy oil and replacing two meat dishes with two fish dishes provides enough n-3 HUFAs to produce a value near the clinical target of 50%, in a manner resembling that seen with traditional Japanese diets. Testing various food combinations with KIM (noted above) readily illustrates that hundreds of different food choices are possible for producing surrogate outcomes ranging from 30% to 90%. The opportunity for change is evident.

References

[14] Lands WEM, Culp BR, Hirai A, Gorman R. Relationship of thromboxane generation to the aggregation of platelets from...


